Pragmatic trials in perioperative medicine: Why, When and How?

Short title: Better randomised trials for better patient care

J. Yeung[1], M.A. Gillies[2] and R.M. Pearse[3].

1. J. Yeung, Warwick Medical School, University of Warwick, UK CV4 7AL
2. M.A. Gillies, Department of Anaesthesia, Critical Care and Pain Medicine, Royal Infirmary of Edinburgh, Edinburgh, UK.
3. R.M. Pearse, Barts and The London School of Medicine & Dentistry, Queen Mary University of London, UK EC1M 6BQ.

Correspondence to:
Rupert Pearse
Adult Critical Care Unit
Royal London Hospital
London
E1 1BB
United Kingdom
e-mail: r.pearse@qmul.ac.uk
Tel: +44 20 3594 0351

Keywords: Pragmatic Randomized Controlled Trials, Perioperative Care, Postoperative care/statistics & numerical data; Postoperative care/methods

Main text: 1893 words

Introduction

We have been asked to write a counter-view to appear alongside an interesting editorial discussing pragmatic trials, particularly in the setting of perioperative care, written by three well respected leaders in our field. We agree that there are common problems with the way randomised trials have been undertaken in the past, especially in anaesthesia and surgery. We also recognise that these problems undermine the value of research as a tool to improve patient care. We propose an alternative view of pragmatic randomised controlled trials in perioperative care and how future research might be improved.

Why should we perform large randomised trials?

Joshi, Alexander and Kehlet highlight the important role that evidence based medicine (EBM) plays in delivering high-quality patient care. While we agree with this view, many clinicians do not.[1] We have known for some time that systematic reviews and meta-analyses may produce discordant results which may in turn be at variance with the findings of large pragmatic RCTs.[2-4] Consequently, the evidence on which we base our clinical practice must range from individual experience, to expert recommendations, and various forms of clinical research. Whilst clinical experience will always form the foundation of EBM, high-quality randomised trials have been placed at the apex of the evidence pyramid. This is not because they are perfect, but because in many cases they offer the best knowledge we have. Nevertheless, ardent proponents of EBM should acknowledge that many clinical questions simply cannot be answered with a randomised trial, either because this would be technically difficult, or because we lack the equipoise to randomise patients to what we believe may be sub-standard care. The refusal of some leading authorities on EBM to acknowledge this point does nothing to help our patients. Meanwhile the frailty of the concept of clinician as infallible expert is widely reported in the mainstream media.[5] Airway management provides a good example of an area of practice where collective clinical experience has evolved an approach to patient care that is effective and safe, in the absence of large clinical trials.[6] Anaesthesia and surgery are craft specialties and naturally weighted towards decisions informed by clinical experience and the trial of n=1. However, to assume that all clinical questions can be resolved in this way is a dangerous mistake.

The tension between the craft of anaesthesia and the need for evidence is not new. John Snow is held in high esteem by both the anaesthetic and public health communities for his technical expertise in developing the craft of anaesthesia, and also his ability to apply epidemiological evidence to inform practice.[7] We encounter many simple questions in our daily practice that can only be answered at a population level. The relative merits of different anaesthetic, analgesic, or muscle relaxant drugs offer

important examples.[8] It is tempting to believe an astute clinician can identify the risks and benefits of these treatments without reference to clinical research, but this view is dangerously unrealistic. Mainstream media is littered with examples of what happens to doctors whose clinical judgement fails them and, consequently, their patients. [9-11] Quality Initiatives such as 'Getting it right first time' have exposed widespread variations in perioperative practice which cannot be justified in terms of patient outcomes or healthcare costs.[12] The intensive care field has recently been enlivened by debate about a retrospective cohort study from a single US medical centre reporting dramatic effects of a cocktail of intra venous vitamin C, hydrocortisone and thiamine on survival amongst patients with sepsis.[13] The lead author has argued that it would be unethical confirm these findings in a randomised trial before starting treatment on septic patients. [14] Society may initially support these exponents of seemingly miraculous treatments, but is no longer prepared to forgive when theories are found to be flawed. We argue that a well-designed and well implemented randomised trial provides the security of knowledge with a low risk of bias, and therefore offers the greatest benefit to our patients.

When should we perform randomised trials?

The decision to offer surgery to a patient must involve consideration of the potential benefit, as well as likely harms. There is growing recognition that we have more work to do in generating high-quality evidence to minimise the harm associated with anaesthesia and surgery, to inform patients and clinicians of risk, and hence maximise the overall benefit. The purpose of pragmatic (or clinical effectiveness) trials is to confirm the benefits of a treatment which has shown promise in smaller explanatory (or efficacy) trials whilst accounting for the practicalities of use in the real world clinical environment. Explanatory trials are designed to answer the question 'Can this treatment work?'; they tend to be small in sample size, with tightly defined inclusion and exclusion criteria, ensuring ideal conditions for the study treatment to work. Pragmatic trials answer the question 'Does this treatment work?' and typically include widely generalisable populations in a large number of hospitals. Pragmatic trials are designed to embrace the variation between patients, doctors and hospitals because this represents the 'usual care' context in which we expect the treatment to work if implemented into routine practice. In reality, this is a continuum, and some trials are more pragmatic than others.[15,16] Perhaps inevitably, the apparent benefits of new treatments are often diluted in pragmatic trials, when factors such as compliance, concomitant therapy and side-effects feature more prominently and diminish the effectiveness of study treatments. If this phenomenon is a reality for our patients, it must be reflected in our assessment of how well a treatment works.

To us it seems obvious that it is important to know when a treatment is not effective in the normal clinical environment. However, some commentators debate the value of large trials which frequently fail to confirm the clinical effectiveness of treatments. The suggestion seems to be that we should somehow only study treatments which will be shown to work, or perhaps not study any treatments at all. There is too much emphasis on trials with 'positive' findings, and the attendant obsession with significant p-values, as opposed to effect estimates and confidence intervals. The wealth of clinical information provided by a well-conducted clinical trial is frequently ignored. This reflects the frustration when, often following years of anticipation, a new treatment simply does not deliver on the initial promise. Similarly, we often struggle to accept that treatments developed from first principles of physiology may sometimes prove to be ineffective. Perhaps our expectations are sometimes unrealistic? Whether the general public, the media or clinician, we all love to hear exciting news about an innovative treatment which will revolutionise treatment of disease. The purpose of pragmatic trials, however, is not to extend knowledge into exciting and novel areas but to enhance the acuity of clinical evidence on an existing question. A well designed clinical trial on an important question can never be 'negative'. These findings ensure patients are no longer exposed to the risks of an ineffective or even harmful treatment, and scarce healthcare resources can be reinvested elsewhere. This concept, sometimes described as de-adoption and exnovation, has an increasingly important place in the delivery of modern healthcare and must not be dismissed. [12,17]

How should we perform randomised trials?

There are numerous challenges to designing and completing a pragmatic trial. The pressure to achieve academic success or work within finite research funding may force investigators to make compromises. Poor choices in terms of inclusion criteria, sample size and clinical outcome measures are commonplace. In many cases, randomised trials fail because researchers fail to either pose a relevant question or to design a trial which is appropriate to answer it. It is crucial that we don't progress to pragmatic trials until we have a sound biological basis for our treatment strategy in terms of dose, timing and patient population. This often means taking several years to conduct smaller explanatory and feasibility trials to provide the information needed to design the optimal large pragmatic trial. The reluctance to thoroughly test biological plausibility, refine the design and study processes of large trials, has been the downfall of many investigators. Futility of the trial might be associated with futility of the treatment, but it can also arise due to a poorly designed trial, inadequate delivery of the study treatment or a lack of eligible patients. Consequently, many promising treatments might be discounted simply because of badly designed trials.

Another common problem with pragmatic trials is a failure to focus on outcomes which are important to patients. Historically, research in anaesthesia and surgery has focused on health status in the immediate (30-day) post-operative period.[18] The vast majority of patients who consent to surgery do not do so simply to be alive 30 days later. Rather, they hope for a return to a desired level of functional independence, or to enjoy a good quality of life for the longest time possible. Patients and the public have much to offer as research partners and their involvement is now rightly seen as a marker of research excellence.[19,20] Pragmatic trials must focus on a small number of clinical outcomes, which are realistically modifiable by the study treatment, and are of direct relevance to patients. This must also include reporting of safety outcomes which for many years were often ignored in our field. The financial impact of treatments must also be considered in the era where it is recognised that wasted resources may actually contribute to harm elsewhere in the healthcare system. The cost of enhanced perioperative care may be more than covered by the financial savings achieved when fewer patients develop complications. Hence, what is good for patient care may be good for the healthcare economy as well. High quality perioperative care has the potential to save money as well as lives.[21,22] To this end, we believe that every major trial of a perioperative treatment should include a cost effectiveness analysis.

Finally, when well conducted, pragmatic trials do produce new knowledge beneficial to patients, we must engage with widespread adoption and implementation at scale, to ensure that patients benefit as quickly as possible. The good pragmatic trial should include a plan for implementation, beginning with the dissemination of knowledge. Clinicians commonly dispute outcome data from studies, not because of limitations in trial design, but because the findings don't fit their own priors, preconceptions and knowledge base. They place emphasis on certain harms but ignore others. Sadly, the anaesthetist's understanding of physiology is often outdated and incorrect, frequently differing widely between clinicians. Sometimes the findings of high-quality research may challenge our beliefs.[23] We must learn to accept unexpected or even unwelcome findings of large trials which have been well designed and conducted. Instead of dismissing results we cannot explain, we must seek to understand why an intervention can benefit or harm patients. We must also be prepared to accept that some benefits or harms are simply not as important as we previously thought.

Conclusions

Patients expect us to use the best possible evidence to determine what their best possible treatment should be. With more than 300 million patients undergoing surgery worldwide each year, the need for high quality clinical trials in perioperative medicine has never been greater. Like all research

methods, pragmatic clinical trials have limitations. Many of these can be avoided through better, more thoughtful trial design. Pragmatic trials cannot provide answers to every important clinical question however, it is unwise to dismiss them or the knowledge they provide.

Conflicts of interest

There was no external funding for this work. RP holds research grants, and has given lectures and/or performed consultancy work for Nestle Health Sciences, BBraun, Medtronic, Glaxo Smithkline, Intersurgical, and Edwards Lifesciences. RP is a member of the Associate editorial board of the British Journal of Anaesthesia and holds a National Institute for Health Research Professorship. JY is supported by National Institute of Health Research Post-Doctoral Fellowship. MG declares no conflicts of interest.

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